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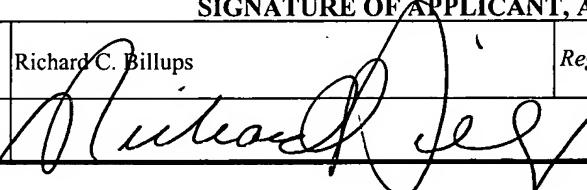
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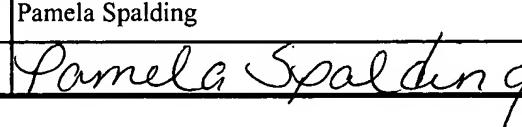
### Remarks

Amended Brief on Appeal.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Name	Richard C. Billups	Registration No. (Attorney/Agent)	31,916
Signature			Date
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants: Joseph L. Duffy, et al.

Serial No: 10/701,186

Filed: November 4, 2003

Customer No: 000210

Confirmation No: 6239 Case No.: 21167

Art Unit: 1626

For: CYANTHOPHENYL DERIVATIVES,  
COMPOSITIONS CONTAINING COMPOUNDS  
AND METHODS OF USE

Examiner:  
Laura L. Stockton

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APPELLANTS' BRIEF ON APPEAL

Sir:

This is an appeal pursuant to 35 U.S.C. § 134 and 37 C.F.R. §§ 41.31 et seq. from the final rejection of claims 14 and 15 mailed on March 6, 2006 in the above identified patent application. Claims 14 and 15 were rejected twice. This Brief is in furtherance of the Notice of Appeal filed in this case on May 22, 2006. Accordingly this brief is timely filed. This brief is submitted in triplicate. The fee for submitting this brief is \$500.00 (37 C.F.R. 1.17(c)), and has already been charged to our deposit account. Please charge Deposit Account No. 13-2755 in the amount of \$500.00 to cover this fee. The Commissioner is hereby authorized to charge any additional fees that may be required for this appeal or to make this brief timely, or credit any overpayment to Deposit Account No. 13-2755.

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MERCK & CO., INC.

by Jane D. Spalding Date 9-28-06



Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 2

## TABLE OF CONTENTS

- I. Real Party in Interest
- II. Related Appeals and Interferences
- III. Status of Claims
- IV. Status of Amendments
- V. Summary of Claimed Subject Matter
- VI. Ground of Rejection to Be Reviewed on Appeal
- VII. Argument
- VIII. Claims Appendix
- IX. Evidence Appendix
- X. Related Proceeding Appendix

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 3

## **I Real Party in Interest**

The real party in interest in this appeal is Merck & Co., Inc. a corporation of the state of New Jersey, and the assignee of the captioned patent application.

## **II Related Appeals and Interferences**

There are no appeals or interferences known to Appellant, his legal representative, or the assignee that will directly affect, will be directly affected by or will have a bearing on the Board's decision in this appeal.

## **III Status of Claims**

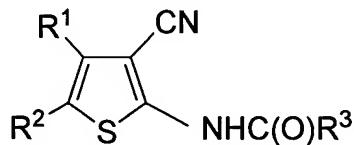
Claims 14, 15, 16, 19 and 20 are presently in the case. Claims 14 and 15 stand finally rejected under 35 U.S.C. §103(a) as obvious in view of Kawai et al, U.S. Patent No. 6,048,880 (Kawai). Claims 16, 19 and 20 were deemed allowable by the Examiner. Appellants hereby appeal the final rejection of claims 14 and 15.

## **IV Status of Amendments**

There were no amendments filed subsequent to the final rejection dated March 6, 2006. Therefore the claims set forth in Appendix A to this brief are those set forth before the final rejection.

## **V Summary of Claimed Subject Matter**

Appellants' invention as presently claimed relates to compounds of formula I:



I

The compounds are 3-cyanothiophenes having an amide attached through a nitrogen atom at position two of the thiophene ring. The compounds are pharmacologically active as glucagon receptor antagonists and are therefore expected to be useful for the treatment of type 2 diabetes.

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 4

Claim 14 addresses 3-substituted cyanothiophenes wherein R<sup>1</sup> represents methyl at position 4 (Specification at page 8, Line 2). A 3-pentyl group is attached to the thiophene nucleus at position 2 through an amide linker (specification at page 8, line 3) and a variety of side groups represented by R<sup>2</sup> can be found at position 5 (specification at page 8, line 4 – page 10, line 1). This is a subset of claim 1 as originally presented, and is fully supported by the specification (specification at page 7, line 35 through page 10, line 2).

Claim 15 addresses a subset of compounds of original claim 1 (specification at page 10, line 3 – page 11, line 29). The compounds recited in this claim are also the subject of the written examples (specification at page 28, line 22 – page 53, line 2).

#### **VI Ground of Rejection to be Reviewed on Appeal**

Claims 14 and 15 were finally rejected under 35 U.S.C. 103 (a) for obviousness over Kawai et al (U.S. Patent No. 6,048,880).

#### **VII Argument**

As Appellants discuss in detail below, the final rejection of claim 14 and 15 is factually unsupported by the single reference relied up, Kawai. It is therefore submitted that the rejection does not meet the burden of presenting a prima facie case of obviousness and therefore unpatentability. For this reason alone, Appellants are entitled to the grant of a patent. In re Oetiker 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

To make out a case of prima facie obviousness, the Examiner must determine that in view of the scope and content of the prior art, the difference between the art and the claims and the level of skill in the art, a reference would at least appear to render the claimed invention obvious to one of ordinary skill. Here, the reference relied upon does not satisfy this requirement.

#### **Structural Differences**

The prior art reference relied upon by the Examiner provides a broad genus that would not have led one of ordinary skill in the direction that Appellants have taken. First, the central ring in the Kawai reference is highly variable. It can represent a furan (X in Kawai represents an oxygen atom), a

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 5

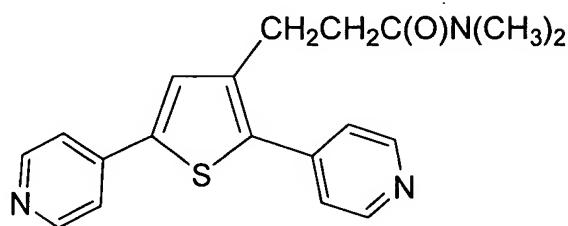
thiophene (X represents sulfur), or an oxidized form of thiophene (X represents a sulfoxyl or sulfonyl group). Moreover, the central ring in Kawai can be fused to a second ring (two of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> in Kawai are taken together and form a group of the formula -A<sup>1</sup>-B<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-B<sup>1</sup>-A<sup>3</sup>-B<sup>2</sup>-A<sup>2</sup>-, which together with the carbon atoms to which A<sup>1</sup> and A<sup>2</sup> are attached, defines an additional fused ring having 4 to 8 ring atoms, with this ring being further optionally substituted.

The preferred groups described in Columns 7 and 8 of Kawai include furan and thiophene compounds where the central furan or thiophene ring is optionally fused to a second ring. No preference is specified in Kawai for thiophene compounds.

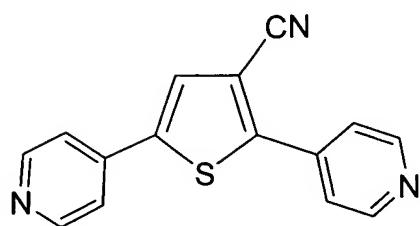
Kawai further requires the presence of a 4-pyridyl group attached to the central aromatic heterocyclic ring, either furan, thiophene, sulfoxyl or a sulfonyl containing ring, at position 2, and is varied at other points of substitution around the ring.

In the final rejection, the Examiner identified the following compounds from Kawai in support of the position that the claims are *prima facie* obvious in view of Kawai:

Example 49 of Kawai

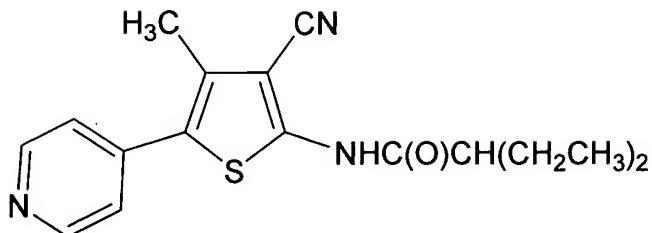


Col. 9, line 19 of Kawai



In claim 14 presently on appeal, the following compound is disclosed:

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 6



The other compounds in the appeal claims are structurally more distant from the compounds of Kawai than the compound shown above.

Nothing within Kawai or any other reference would have taught or would have appeared to suggest to the ordinarily skilled artisan to delete one of the two pyridyl rings shown in Example 49 or Col. 9, line 19 of Kawai, to reverse the linkage to the thiophene such that the alkyl chain is linked to the thiophene through the amide nitrogen atom instead of a carbon atom, or to replace the dimethylpropionamide group found in the compound of example 49 with a cyano group, and to place a 3-pentyl group at position 2 of the central thiophene ring linked through an amide moiety.

The structural differences between Appellants' claimed invention and the Kawai reference are therefore urged to be clear and in favor of a finding that no *prima facie* obviousness exists with respect to claims 14 and 15.

The Examiner has urged that Kawai teach thiophene compounds that are structurally similar to the instantly claimed compounds, and that the instantly claimed compounds are generically described in Kawai. The selection of –CN, R<sup>1</sup> representing CH<sub>3</sub>, and R<sup>3</sup> representing 3-pentyl positioned as recited in claim 14 on a thiophene central ring does not constitute an “indiscriminate” selection of “some among many” substituent groups, as described in *In re Lemlin* 141 U.S.P.Q. 814 (CCPA 1964). In *Lemlin*, the claims were allowed because the choice of a specified number of total carbon atoms was critical and imparted a special significance to the compounds, i.e., the compounds that were claimed were selective and potent herbicides. Lemlin successfully demonstrated that absent the critical number of carbon atoms, greater than 5, the compounds exhibited no significant herbicidal activity against crabgrass.

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 7

### Differences in Properties

In the present case, there are distinctly different and unexpected properties embodied in the compounds of the claims relative to Kawai. Yet, the Examiner has alleged that the existence of the genus of Kawai would render the species claimed *prima facie* obvious, and that one of ordinary skill would have been motivated by virtue of similar activities (cytokine production inhibitor).

The Kawai compounds are alleged to be useful as inhibitors of the production of inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , and are therefore allegedly useful to treat inflammatory disorders.

The compounds that are claimed by Appellants have a distinctly different activity, functioning as glucagon receptor antagonists. Appellants dispute that the claimed compounds and the Kawai reference therefore disclose compounds which would "possess similar activity" as alleged by the Examiner. Inhibiting cytokine production is not similar to antagonizing the glucagon receptor, when evaluated from the perspective of one ordinarily skilled in the art.

Moreover, a perceived similarity between utilities does not negate unexpectedness in the property discovered. The glucagon receptor antagonist activity discovered could in fact be very similar to the alleged utility disclosed in Kawai and still qualify as a property which is unexpected in view of Kawai. Nothing within Kawai (or any other reference) would have negated unexpectedness in the glucagon receptor antagonist property. Hence, *prima facie* obviousness based upon similar activities does not exist.

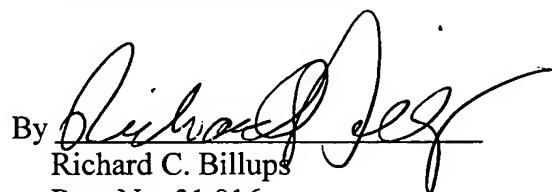
It is well known that a chemical compound is comprised of its structure and the properties embodied therein; the two cannot be separated. In re Papesh 137 U.S.P.Q. 43 (CCPA 1963). The structural differences taken in combination with the difference in activities does not support a case of *prima facie* obviousness. For the above reasons, Appellants respectfully submit that the final rejection of claim 14 and 15 is in error and should be reversed.

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 8

**Conclusion**

In conclusion, Appellants respectfully submit that the final rejection of claims 14 and 15 is in error and should be reversed.

Respectfully submitted,

By 

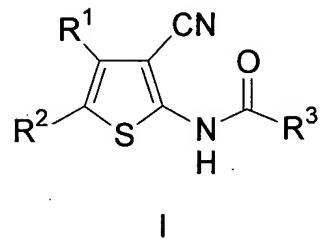
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Date: *September 26, 2006*

**VIII. Claims Appendix**

**Appendix A**

Claim 14. A compound of the formula I:



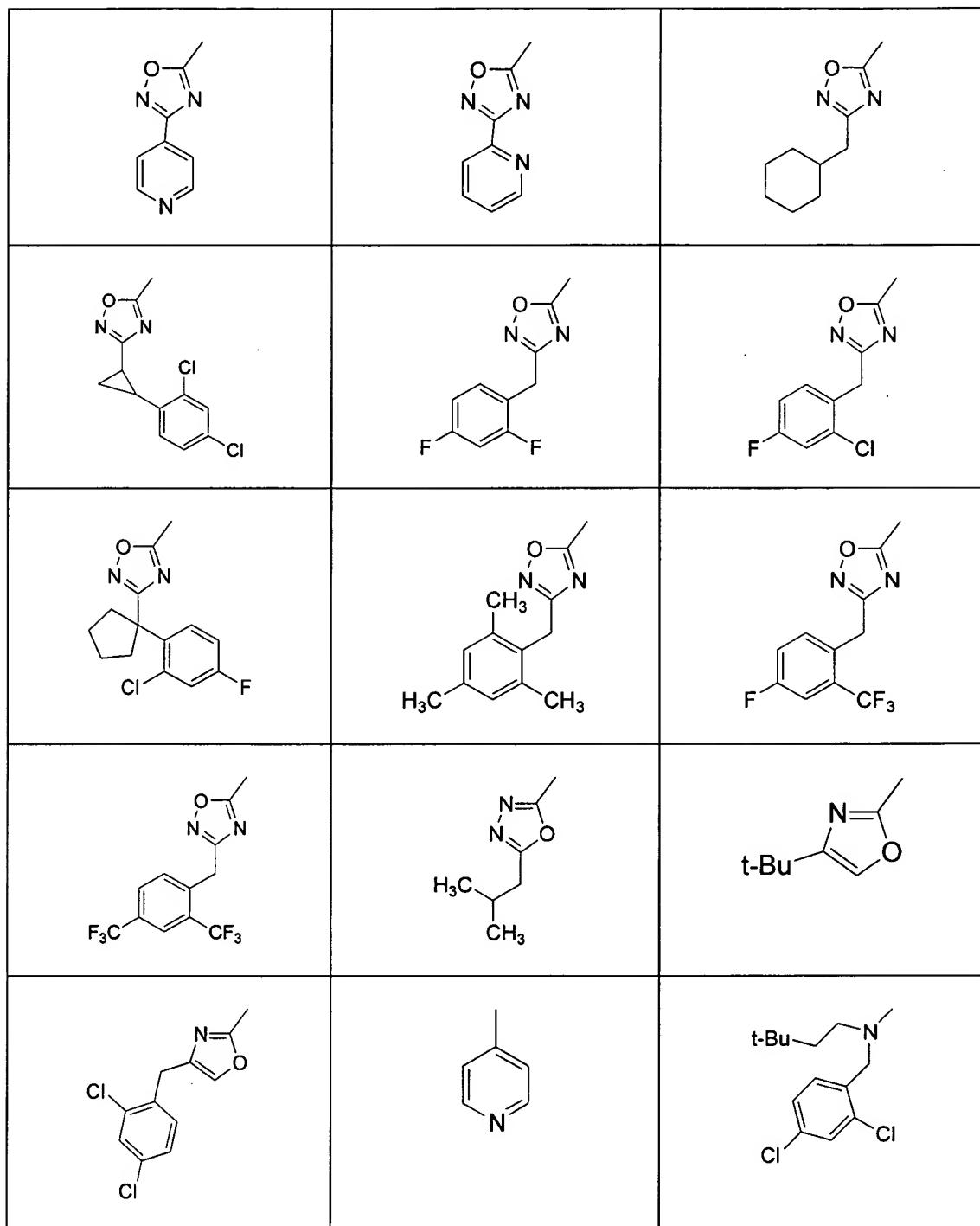
wherein:

R<sup>1</sup> represents methyl;

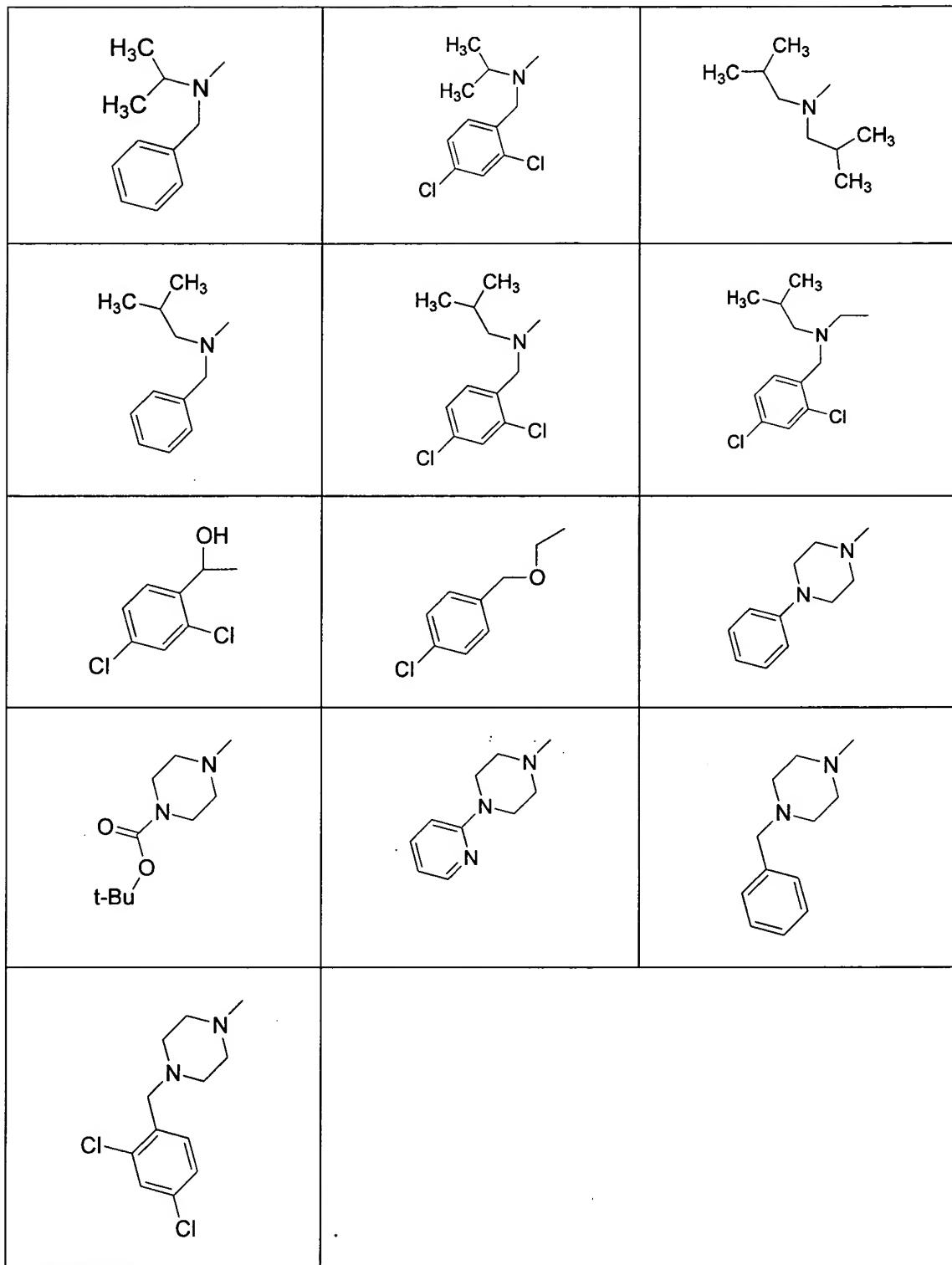
R<sup>3</sup> represents 3-pentyl, and R<sup>2</sup> is selected from the table below:

R <sup>2</sup>		

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 10



Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 11



Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 12

Claim 15. A compound selected from the group consisting of:

N-[3-cyano-5-(3-isobutyl-1,2,4-oxadiazol-5-yl)-4-methylthien-2-yl]-2-ethylbutanamide;  
N-{3-cyano-5-[3-(2,4-dichlorobenzyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-[5-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;  
N-[5-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;  
N-[3-cyano-4-methyl-5-(3-phenyl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
N-[3-cyano-4-methyl-5-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
N-[3-cyano-4-methyl-5-(3-pyridin-3-yl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
N-[3-cyano-4-methyl-5-(3-pyridin-4-yl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
N-{3-cyano-5-[3-(cyclohexylmethyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-(3-cyano-5-{3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}-4-methylthien-2-yl)-2-ethylbutanamide;  
N-{3-cyano-5-[3-(2,4-difluorobenzyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-{5-[3-(2-chloro-4-fluorobenzyl)-1,2,4-oxadiazol-5-yl]-3-cyano-4-methylthien-2-yl}-2-ethylbutanamide;  
N-(5-{3-[1-(2-chloro-4-fluorophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}-3-cyano-4-methylthien-2-yl)-2-ethylbutanamide;  
N-{3-cyano-5-[3-(mesitylmethyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-(3-cyano-5-{3-[4-fluoro-2-(trifluoromethyl)benzyl]-1,2,4-oxadiazol-5-yl}-4-methylthien-2-yl)-2-ethylbutanamide;  
N-(5-{3-[2,4-bis(trifluoromethyl)benzyl]-1,2,4-oxadiazol-5-yl}-3-cyano-4-methylthien-2-yl)-2-ethylbutanamide;  
N-[3-cyano-5-(5-isobutyl-1,3,4-oxadiazol-2-yl)-4-methylthien-2-yl]-2-ethylbutanamide;  
N-[5-(4-tert-butyl-1,3-oxazol-2-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;  
N-{3-cyano-5-[4-(2,4-dichlorobenzyl)-1,3-oxazol-2-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-(3-cyano-4-methyl-5-pyridin-4-ylthien-2-yl)-2-ethylbutanamide;  
N-{3-cyano-5-[(2,4-dichlorobenzyl)(3,3-dimethylbutyl)amino]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-{5-[benzyl(isopropyl)amino]-3-cyano-4-methylthien-2-yl}-2-ethylbutanamide;  
N-{3-cyano-5-[(2,4-dichlorobenzyl)(isopropyl)amino]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-[3-cyano-5-(diisobutylamino)-4-methylthien-2-yl]-2-ethylbutanamide;  
N-{5-[benzyl(isobutyl)amino]-3-cyano-4-methylthien-2-yl}-2-ethylbutanamide;

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 13

N-{3-cyano-5-[(2,4-dichlorobenzyl)(isobutyl)amino]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-{3-cyano-5-[(2,4-dichlorophenyl)(hydroxy)methyl]-4-methylthien-2-yl}-2-ethylbutanamide;  
N-(3-cyano-5-[(2,4-dichlorobenzyl)(isobutyl)amino]methyl)-4-methylthien-2-yl)-2-ethylbutanamide;  
N-[3-cyano-4-methyl-5-(4-phenylpiperazin-1-yl)thien-2-yl]-2-ethylbutanamide;  
tert-butyl 4-{4-cyano-5-[(2-ethylbutanoyl)amino]-3-methylthien-2-yl}piperazine-1-carboxylate;  
N-[3-cyano-4-methyl-5-(4-pyridin-2-ylpiperazin-1-yl)thien-2-yl]-2-ethylbutanamide;  
N-[5-(4-benzylpiperazin-1-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;  
N-{3-cyano-5-[4-(2,4-dichlorobenzyl)piperazin-1-yl]-4-methylthien-2-yl}-2-ethylbutanamide; and  
N-(5-[(4-chlorobenzyl)oxy]methyl)-3-cyano-4-methylthien-2-yl)-2-ethylbutanamide, as well as the  
pharmaceutically acceptable salts and solvates thereof.

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 14

IX. **Evidence Appendix**

NONE

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 15

X. **Related Proceeding Appendix**

NONE